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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,340	04/01/2005	Robert Y.L. Tsai	4239-66642-05	5503

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EXAMINER	
PITRAK, JENNIFER S	
ART UNIT	PAPER NUMBER
1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,340	TSAI ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-54,56-62 and 64-66* is/are pending in the application.

4a) Of the above claim(s) *41,53,54,59,60,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,42-52,56-58,61,62 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/01/2005; 12/22/2005; 01/05/2006; 09/18/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 40-66 are pending.

Applicants elected Group I, claims 23-36 and 40-62 in the response filed on 9/18/2007 and elected the species, small inhibitory RNA, in the response filed 03/18/2008.

Claims 41, 53, 54, 59, 60, 64, and 65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 03/18/2008.

Claims 40, 42-52, 55-58, 61-63, and 66 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40, 43-51, 56-58, and 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are to methods of inducing senescence of a cell by altering the level of nucleostemin polypeptide in the cell *in vitro* and in a subject, wherein altering comprises

administering an agent that alters the level of nucleostemin. Altering the level of nucleostemin polypeptide includes both increasing and decreasing the level of nucleostemin polypeptide. The agents useful for altering nucleostemin levels are numerous and varied and, as disclosed in the instant specification at page 10, include any polypeptide, compound, small molecule, organic compound, salt, polynucleotide, or other molecule of interest. The agents of the claims further include, for example, agents that interfere with the interaction of nucleostemin with p53 (see p.54 of the instant specification), agents that increase the transcription of nucleostemin mRNA, and agents that decrease the expression of nucleostemin mRNA (claims). The subgroup of agents that interfere with nucleostemin-p53 interaction itself is large and varied, as described in the instant specification at pages 55-56 as follows (emphasis added).

> Page 55, line 25 to page 56, line 4
> Examples of agents that interfere with an interaction of p53 and a nucleostemin, identified using such an assay, include: **chemical compounds; fragments and fusions of nucleostemin; peptidomimetics; antibodies; synthetic ligands that bind nucleostemin or p53, agents which cause the disassociation of p53 and nucleostemin; appropriate nucleostemin or p53 fragments, or other fragments of the natural or synthetic ligands or chemical compounds which bind to p53 and prevent the interaction of p53 and nucleostemin**, and thereby affect cell differentiation, proliferation, and/or senescence. The determination and isolation of ligand/compositions is well described in the art. See, e.g., Lerner, Trends Neuro. Sci. 17:142-146, 1994.
>
> The test compound may also be a **combinatorial library for screening a plurality of compounds.** ...
>
> Page 56, lines 22-24
> Drug candidates are added to the assay wells to determine whether **any agent, such as a chemical compound, antibody or peptide,** blocks binding of p53 to the matrices or plates that contain the nucleostemin.

The claims encompass a large and varied group of methods involving a multitude of agents.

The specification provides two examples of agents that reduce CNS stem cell and U2OS cell proliferation, siRNAs to nucleostemin and a plasmid designed to overexpress nucleostemin

(examples 6 and 7, pages 63-65). Example 6 indicates siRNAs to nucleostemin reduce nucleostemin levels and reduce cell proliferation in two cell types. Example 7 is not clear as to whether the introduced plasmid actually overexpresses nucleostemin, as expected, or if the plasmid may be interfering with nucleostemin gene expression, as was reported for chalcone synthase gene overexpression in petunia plants by Napoli, *et al.* (1990, The Plant Cell, v.2:279-89; abstract). Thus, the specification provides a description of siRNA inhibitors of nucleostemin. The specification does not provide a description of the full range of agents that alter the level of nucleostemin and induce senescence.

The art describes nucleic acid inhibitors of nucleostemin gene expression as effective for reducing tumor cell proliferation, as is evident from Kennedy, *et al.* (2003/0008284, filed 06/15/2001, item #1 on 04/01/2005 IDS), who teach antisense- and ribozyme-mediated reduction in tumor cell proliferation. (See rejection under 35 U.S.C. § 102(e) below.) The art does not describe other agents that inhibit or increase nucleostemin levels and induce cell senescence.

Both the specification and the art do not describe the full breadth of agents that increase the level of nucleostemin, nor do they describe the full breadth of agents that decrease nucleostemin levels. Agents that increase transcription of the nucleotide sequence encoding nucleostemin, such as plasmids for overexpression, are known. However, this is not representative of the genus of agents useful for increasing nucleostemin levels, which encompasses agents that can indirectly influence the level of nucleostemin, such as transcription factors for the nucleostemin gene. Likewise, the known agent, a nucleostemin siRNA, is not representative of the genus of agents useful for decreasing nucleostemin levels because a nucleostemin siRNA does not lead one of skill in the art to envision the structure of other

inhibitors, such as small molecules, for example. Therefore, the claims clearly lack sufficient description of the essential structure required for the claimed functions.

Furthermore, the specification and the art also do not describe the full breadth of the genus of target polypeptides. The claims are to a method comprising altering the level of a nucleostemin polypeptide having at least 80% amino acid sequence identity to SEQ ID NO: 6. The 20% of amino acids that can be changed and still provide a nucleostemin polypeptide is not known, nor are they described in the instant specification. The structure of those polypeptides with 80% identity to SEQ ID NO: 6 that, upon altering the levels of these polypeptides, induce cell senescence is not known nor described. There is a lack of correlation between the proteins with 80% identity to SEQ ID NO: 6 and the function of inducing senescence upon altering the level of those proteins.

Claims 40, 42-52, 56-58, 61, 62, and 66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing senescence in CNS stem cells and U2OS cells by administration *in vitro* of an siRNA targeting the nucleostemin gene, does not reasonably provide enablement for inducing senescence in any cell type by administering any agent that may increase or decrease nucleostemin protein levels. The specification does not enable one of skill in the art to induce senescence of cells *in vivo* by any means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the following factors enumerated *In re Wands*, 8 USPQ2d

1400, at 1404 (CAFC 1988) are considered: (1) the breadth of the claims, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the quantity of experimentation necessary. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The claims are to methods of inducing senescence of a cell *in vitro* and *in vivo* comprising altering the level of nucleostemin polypeptide by administering any agent that increases or decreases nucleostemin levels. Claims 52, 61, and 66 more specifically claim methods comprising administering an siRNA targeting nucleostemin.

The specification teaches the cloning of the nucleostemin gene, nucleostemin protein expression and cellular distribution, and that siRNAs targeting nucleostemin reduce nucleostemin protein levels and disrupt proliferation of the siRNA-treated cells (Figures 1-5, pages 3-6 and 57-64). The specification teaches that cells treated with a plasmid designed for overexpression of nucleostemin also demonstrate disrupted proliferation (example 7, pp.64-5). However, the specification does not confirm the overexpression of nucleostemin with the administration of the plasmid of example 7. While the specification contemplates use of agents such as polypeptides, compounds, small molecules, organic compounds, salts, polynucleotides, or other molecules of interest for altering levels of any protein of interest, (see page 10 and pages 55-6), the specification does not demonstrate induction of senescence in cells by any means other than with a particular siRNA (SEQ ID NO: 7) or plasmid *in vitro* (Examples 6 and 7, p.63-5). The specification provides no guidance indicating which of all the possible agents will increase

or decrease nucleostemin levels or guidance of how to determine which agents will increase or decrease nucleostemin levels. Furthermore, the specification does not demonstrate any *in vivo* examples of inducing senescence of cells in a subject.

The art provides no guidance to enable the instant claims, beyond the *in vitro* use of a nucleic acid inhibitor of nucleostemin expression. The art does not enable methods of inducing cell senescence by administering any agent that increases or decreases nucleostemin levels. As described above, all of the inhibitors and activators of polypeptides with 80% identity to SEQ ID NO: 6 are not known nor described so as to enable one of skill to make and use the invention. Furthermore, The *in vivo* use of siRNAs is well-recognized as severely limited by challenges with administration and delivery. For instance, in a recent report, Nguyen, *et al.* (2008, Cur. Op. Mol. Therap., v.10:158-67) teach that "the major challenges for the development of RNAi-based therapeutics are administration and delivery," (p.158, column 2). At p.159, first column, Nguyen, *et al.* further indicate that the majority of clinical trials with siRNA therapeutics are those in which the siRNA is injected or inhaled directly into target organs and further that systemic delivery is more challenging because of rapid degradation of siRNAs in the serum and by renal filtration.

Thus, the claims are not enabled for their full scope due to severe deficiencies in the amount of guidance and predictability for performing the claimed methods are provided by the art and by the instant specification. Practice of the claimed methods to their full scope would require undue experimentation because all of the possible agents that will increase or decrease nucleostemin levels and induce cell senescence are not known and are not predictable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 40, 42, 43, 46-51, 56-58, and 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Kennedy, et al. (2003/0008284, filed 06/15/2001, item #1 on 04/01/2005 IDS) ("Kennedy").

The claims are directed to a method of inducing senescence of a cell or tumor cell in a subject by increasing or decreasing the level of nucleostemin polypeptide, wherein the nucleostemin polypeptide is at least 80% identical to SEQ ID NO: 6. Claim 46 is to the method wherein the nucleostemin polypeptide comprises SEQ ID NO: 10, which is the consensus amino acid sequence for SEQ ID NOs: 2, 4, and 6.

Kennedy discloses and claims a method of inhibiting tumor growth in a subject by administering an agent that decreases activity of the gene product encoded by SEQ ID NO: 22 (claim 18). SEQ ID NO: 22 encodes the polypeptide, SEQ ID NO: 23, which is 100% identical to the instantly claimed SEQ ID NO: 6 (p.25, Table 2; p.59). Kennedy also claims a method for suppressing or inhibiting a cancerous phenotype by introducing into a mammalian cell an antisense polynucleotide for inhibiting expression of SEQ ID NO: 22 (claim 14). At page 11, paragraph 0116, Kennedy teaches that ribozymes, antisense constructs, and dominant negative mutants can be used to inhibit gene expression of the genes of the invention, which include SEQ

ID NO: 22 (p.2, paragraph 0012), and that ribozymes can be used to inhibit gene expression *in vivo* or *in vitro* (pp.11-12, paragraph 0119). At paragraph 0232 (p.22), Kennedy teaches that the compositions of the invention can be delivered via ex vivo applications including stem cells. Kennedy teaches the instantly claimed steps of decreasing expression of nucleostemin and administering nucleostemin inhibitors to a subject. It is assumed, absent evidence to the contrary, that such steps would result in the instantly claimed induction of senescence of the cell(s).

Thus, Kennedy clearly anticipates the instant claims 40, 42, 43, 46-51, 56-58, and 62.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40, 42-51, 56-58, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennedy.

The claims are directed to a method of inducing senescence of a cell or tumor cell in a subject by administering a small inhibitory RNA targeting nucleostemin that decreases the level of nucleostemin polypeptide, wherein the nucleostemin polypeptide is at least 80% identical to SEQ ID NO: 6, comprises SEQ ID NO: 6, comprises SEQ ID NO: 4, comprises SEQ ID NO: 2, or comprises SEQ ID NO: 10. SEQ ID NO: 10 is the consensus amino acid sequence for SEQ

ID NOs: 2, 4, and 6. SEQ ID NO: 2 is the rat homolog of SEQ ID NO: 6. SEQ ID NO: 4 is the mouse homolog of SEQ ID NO: 6.

Kennedy teaches the inhibition of nucleostemin as described above under the rejection under 35 U.S.C. 102(e). Kennedy further discloses that the invention encompasses homologs corresponding to SEQ ID NO: 22, where the source of homologous genes can be rat or mouse (p.5, paragraph 0056). These homologous sequences can be readily identified by one skilled in the art as described at p.5, paragraph 0053.

It would have been obvious to inhibit the expression of mouse and rat nucleostemin because Kennedy teaches and claims inhibition of human nucleostemin and because mouse and rat homologs of nucleostemin are encompassed by Kennedy's invention. Kennedy provides instruction on how one of skill in the art could identify such homologs. One would desire to inhibit nucleostemin in rats and mice because such animals are well-known and routinely used by those of skill in the art as model organisms for studying human conditions and diseases. Therefore, the claims would have been obvious at the time of the instant application.

Claims 40, 42-51, 56-58, 61, 62, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennedy as applied to claims 40, 42-51, 56-58, and 62 above, and further in view of Bass (2001, Nature v.411:428-9).

The claims are directed to a method of inducing senescence of a cell or tumor cell in a subject by administering a small inhibitory RNA targeting nucleostemin that decreases the level of nucleostemin polypeptide, as described above. Claims 61 and 66 specify that the inhibitory agent is a small inhibitory RNA (siRNA).

Kennedy teaches inhibiting nucleostemin using ribozymes and antisense oligonucleotides as described above. Kennedy does not teach inhibiting nucleostemin using siRNAs.

Bass teaches that RNAi is more robust than antisense techniques in that it works more often and typically decreases expression of a gene to lower levels, or eliminates it entirely and that siRNAs are effective at concentrations that are several orders of magnitude lower than the concentrations typically used in antisense experiments (top of p. 429).

It would have been obvious to use siRNAs as nucleostemin inhibitors for the instantly claimed methods of decreasing nucleostemin levels. Kennedy teaches the use of antisense for nucleostemin inhibition. Bass provides a reason to use siRNAs in place of antisense by teaching that siRNA inhibition is better than antisense-mediated inhibition. Thus, claims 40, 42-51, 56-58, 61, 62, and 66 would have been obvious to one of skill in the art at the time of the instant application.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak, PhD
Examiner, Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635